EXPRESS SCRIPTS®

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hematology – Gene Therapy – Lyfgenia UM Medical Policy
- Lyfgenia® (lovotibeglogene autotemcel intravenous infusion – bluebird bio)

REVIEW DATE: 02/11/2026

OVERVIEW

Lyfgenia, an autologous hematopoietic stem cell-based gene therapy, is indicated for the treatment of **sickle cell disease** in patients ≥ 12 years of age with a history of vaso-occlusive events (VOEs).[1] Limitation of Use. Following treatment with Lyfgenia, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell (RBC) transfusions. Lyfgenia has not been studied in patients with more than two α-globin gene deletions.

Lyfgenia is given as a single dose (once per lifetime), which contains a minimum of 3 x 10^6 cluster of differentiation 34+ (CD34+) cells/kg of body weight.[1] Lyfgenia is given as an intravenous (IV) infusion. The manufacturing time for Lyfgenia takes between 10 to 15 weeks. However, the entire process can take 6 months or longer as patients need to undergo mobilization and apheresis procedures and myeloablative conditioning prior to Lyfgenia infusion.

Lyfgenia is prepared with the patient's own hematopoietic stem cells, which are collected via apheresis procedure(s).[1,2] The CD34+ cells collected from the patient are transduced *ex vivo* with BB305 lentiviral vector (BB305 LVV). The BB305 LVV encodes a modified β-globin gene, which ultimately results in the production of HbA^{T87Q}, a modified adult hemoglobin (HbA). HbA^{T87Q} maintains 99.9% identity to HbA and has a similar oxygen-binding affinity as that of HbA; the difference is that HbA^{T87Q} is designed to inhibit polymerization of the sickle hemoglobin.

Disease Overview

Sickle cell disease is a group of inherited RBC disorders characterized by the presence of a mutated hemoglobin (Hb) subunit beta gene.[3-6] Healthy RBCs are round and contain Hb. In contrast, in a patient with sickle cell disease, RBCs are sickle-shaped and die early, resulting in a constant shortage of RBCs. Furthermore, the sickle-shaped RBCs aggregate in the bloodstream, causing vaso-occlusion, which deprive downstream tissues of nutrients and oxygen, resulting in tissue ischemia, organ damage, and hemolysis (which leads to anemia). In the US, approximately 100,000 persons have the condition and it is estimated 20,000 patients have severe sickle cell disease.[3,7]

Patients with severe sickle cell disease have one of the following genotypes: β^S/β^S, β^S/β^0, β^S/β^+.[3-5] These patients have recurrent vaso-occlusive crises/VOEs, while receiving appropriate supportive care (e.g., pain management, hydroxyurea). Management of sickle cell disease focuses on preventing and treating pain episodes and other complications; symptomatic treatment includes use of analgesics, fluids (hydration), oxygen supplementation, and blood transfusion.[3,5,6] Allogeneic hematopoietic stem cell transplantation (HSCT) requires a stem cell donor, typically a human leukocyte antigen (HLA)-matched donor; less than 20% of patients with sickle cell disease have a suitable donor.[7] Pharmacologic treatments for sickle cell disease include Adakveo® (crizanlizumab-tmca IV infusion), L-glutamine oral powder (Endari®, generic), hydroxyurea, and Oxbryta® (voxelotor tablets and tablets for oral suspension) [no longer available].[8-12]

Clinical Efficacy

The efficacy of Lyfgenia was studied in a single-arm, 24-month, open-label, multicenter Phase I/II study involving adolescents and adults with sickle cell disease.[1,2] In total, there were 36 patients who underwent apheresis after mobilization with plerixafor and received myeloablative conditioning with busulfan and Lyfgenia infusion.[1] Of the 36 patients, 32 patients met the criteria for the "transplant population for VOE efficacy outcomes", which included patients who met the VOE requirement; this population was used to analyze the efficacy endpoints. Patients were eligible to enroll if they had one of the following sickle cell disease genotypes: β^S/β^S, β^S/β^0, or β^S/β^+. However, all patients had the β^S/β^S genotype. In addition, the patients had at least four (protocol-defined) severe VOEs in the 24 months before enrollment and had to have failed hydroxyurea treatment or have intolerance to hydroxyurea. A VOE was defined as any of the following events requiring evaluation at a medical facility: an episode of acute pain with no medically determined cause other than vaso-occlusion and lasting > 2 hours; acute chest syndrome; acute hepatic sequestration; and acute splenic sequestration. Severe VOEs were defined as either a VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and requiring IV medications at each visit OR priapism requiring any level of medical attention. Key exclusion criteria were patients with the following: clinically significant and active bacterial, viral, fungal, or parasitic infection; advanced liver disease; history or presence of Moyamoya disease; and prior or current malignancy or myeloproliferative disorder or significant immunodeficiency disorder. The median age of the patients was 25 years; 25% of the patients were adolescents (≥ 12 years to < 18 years of age). The primary efficacy endpoint was complete resolution of severe VOEs; the investigators also reported complete resolution of VOEs. Both outcomes were assessed between 6 and 18 months after Lyfgenia infusion. In total, 94% of patients (n = 30/32) had complete resolution of severe VOEs and 88% of patients (n = 28/32) had complete resolution of VOEs.

Guidelines

Sickle cell disease guidelines have not incorporated gene therapies following their FDA approval. The American Society of Hematology (ASH) released evidence-based recommendations for stem cell transplantation for patients with sickle cell disease in 2021.[13] ASH notes that it is unclear how gene therapies will affect sickle cell disease outcomes, including organ complications and if broader access to curative therapy will alter the trajectory of sickle cell disease outcomes. ASH notes that while success rates after allogeneic HSCT are increasing, survival rates in patients receiving disease-modifying medications (e.g., hydroxyurea, L-glutamine, Adakveo, Oxbryta [no longer available]) and supportive care are also improving. More than 90% of patients who have undergone HSCT (predominantly using HLA-identical family donors) have been cured of sickle cell disease, as reported in short-term follow-up. Allogeneic HSCT is an established therapeutic option for patients with sickle cell disease with a clinical indication and an HLA-identical family donor. However, for the majority of patients, there are no suitable donors.

Safety

Lyfgenia has a Boxed Warning regarding hematologic malignancy.[1] At the time of initial product approval, two patients treated with an earlier version of Lyfgenia using a different manufacturing process and transplant procedure developed acute myeloid leukemia and one patient with an α-thalassemia trait was diagnosed with myelodysplastic syndrome. Patients should be monitored for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Lyfgenia. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Because of the specialized skills required for evaluation and diagnosis of patients treated with Lyfgenia as well as the specialized training required for administration of Lyfgenia, approval requires Lyfgenia to be prescribed by a physician who specializes in the condition being treated. All approvals are provided for one-time (per lifetime) as a single dose. The approval duration is 1 year to allow for an adequate timeframe to prepare and administer one dose of therapy. If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. For the dosing criteria, verification of the appropriate weight-based dosing is required by a Medical Director as noted by **[verification required]**. In the criteria for Lyfgenia, as appropriate, the symbol (†) is noted next to the specified gender. In this context, the specified gender is defined as follows: females/males are defined as individuals with the biological traits of a woman/man, regardless of the individual's gender identity or gender expression.

All reviews (approvals and denials) will be forwarded to the Medical Director for evaluation. Some clients have elected Embarc Benefit Protection. For these clients, the Medical Director will coordinate with EviCore to ensure the Embarc Benefit Protection portion of the review has been completed. If the Embarc Benefit Protection portion of the review has not been completed, the Medical Director will route to Embarc@EviCore.com prior to completing the review.

Documentation: Documentation is required for use of Lyfgenia as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory results, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Lyfgenia is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Sickle Cell Disease.** Approve a one-time (per lifetime) single dose if the patient meets ALL of the following (A, B, C, D, E, F, G, H, I, J, K, L, M, N, and O):
   - **A)** Patient is ≥ 12 years of age; AND
   - **B)** Patient has not received a gene therapy for sickle cell disease in the past **[verification in claims history required]**; AND
     Note: If no claim for Lyfgenia or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Lyfgenia or Casgevy.
   - **C)** According to the prescribing physician, a hematopoietic stem cell transplantation is appropriate for the patient; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** Patient does not have a Human Leukocyte Antigen (HLA)-matched donor; OR
     - **ii.** Patient has an HLA-matched donor, but the individual is not able or is not willing to donate; AND
   - **E)** Genetic testing **[documentation required]** indicates the patient has ONE of the following sickle cell disease genotypes (i, ii, or iii):

i. β^S/β^S genotype; OR
ii. β^S/β^0 genotype; OR
iii. β^S/β^+ genotype; AND
Note: Other genotypes will be reviewed by the Medical Director on a case-by-case basis.

F) Patient has tried at least ONE pharmacologic treatment for sickle cell disease **[documentation required]**; AND
Note: Examples of pharmacologic treatment for sickle cell disease include hydroxyurea, L-glutamine, Adakveo (crizanlizumab-tmca intravenous infusion), and Oxbryta (voxelotor tablets and tablets for oral suspension) [no longer available].

G) While receiving appropriate standard treatment for sickle cell disease, patient had at least four severe vaso-occlusive crises or events in the previous 2 years **[documentation required]**; AND
Note: Examples of severe vaso-occlusive crises or events include the following:
- An episode of acute pain that resulted in a visit to a medical facility which required administration of an intravenous opioid and/or intravenous nonsteroidal anti-inflammatory drug;
- Acute chest syndrome, which is defined by the presence of a new pulmonary infiltrate associated with pneumonia-like symptoms (e.g., chest pain, fever [> 99.5°F], tachypnea, wheezing or cough, or findings upon lung auscultation);
- Acute hepatic sequestration, which is defined by a sudden increase in liver size associated with pain in the right upper quadrant, abnormal results of liver function test not due to biliary tract disease, and the reduction of hemoglobin concentration by ≥ 2 g/dL below the baseline value;
- Acute splenic sequestration, which is defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥ 2 g/dL below the baseline value;
- Acute priapism lasting > 2 hours and requiring a visit to a medical facility.

H) Patient does not have the following (i, ii, iii, iv, and v):
i. More than two α-globin gene deletions **[documentation required]**; AND
ii. Clinically significant and active bacterial, viral, fungal, or parasitic infection; AND
iii. Advanced liver disease **[documentation required]**; AND
Note: Examples of advanced liver disease include alanine transaminase > 3 times upper limit of normal; direct bilirubin value > 2.5 times upper limit of normal; baseline prothrombin time (international normalized ratio [INR]) > 1.5 times upper limit of normal; cirrhosis; bridging fibrosis; or active hepatitis.
iv. Severe cerebral vasculopathy as defined by history of untreated Moyamoya disease or presence of Moyamoya disease that puts the patient at risk of bleeding, per the prescribing physician; AND
v. Prior or current malignancy, myeloproliferative disorder, or significant immunodeficiency disorder; AND

I) According to the prescribing physician, patient will have been discontinued from the following medications (for the duration noted) prior to mobilization (i, ii, iii, and iv):
i. Disease-modifying therapies for sickle cell disease for at least 2 months; AND
Note: Examples of disease-modifying therapies for sickle cell disease include hydroxyurea, Adakveo, L-glutamine, and Oxbryta (no longer available).
ii. Erythropoietin for at least 2 months; AND
iii. Iron chelation therapy for at least 7 days; AND
Note: Examples of iron chelators used for this condition include deferoxamine injection, deferiprone tablets or solution, and deferasirox tablets.
iv. Antiretrovirals (prophylactic for human immunodeficiency virus [HIV]) for at least 1 month; AND

Note: Examples of antiretrovirals for HIV include abacavir, emtricitabine, lamivudine, and zidovudine.

J) According to the prescribing physician, patient meets ALL of the following (i, ii, iii, and iv):
- **i.** Patient will undergo mobilization, apheresis, and myeloablative conditioning; AND
- **ii.** A hematopoietic stem cell mobilizer will be utilized for mobilization; AND
  Note: Mozobil (plerixafor subcutaneous injection) is an example of a hematopoietic stem cell mobilizer.
- **iii.** Busulfan will be used for myeloablative conditioning; AND
- **iv.** Sickle hemoglobin level will be < 30% of total hemoglobin with total hemoglobin concentration ≤ 11 g/dL at BOTH of the following timepoints (a and b):
  - **a)** Prior to planned start of mobilization; AND
  - **b)** Until initiation of myeloablative conditioning; AND

K) Patient screening is negative for ALL of the following (i, ii, iii, and iv):
- **i.** Human immunodeficiency virus-1 and -2 **[documentation required]**; AND
- **ii.** Hepatitis B virus **[documentation required]**; AND
  Note: A patient who has been vaccinated against hepatitis B virus (HBV) [HBV surface antibody-positive] who is negative for other markers of prior HBV infection (e.g., negative for HBV core antibody) is eligible; a patient with past exposure to HBV is also eligible as long as patient is negative for HBV DNA.
- **iii.** Hepatitis C virus **[documentation required]**; AND
- **iv.** Human T-lymphotrophic virus-1 and -2 **[documentation required]**; AND

L) According to the prescribing physician, a patient of reproductive potential meets ONE of the following (i or ii):
- **i.** A female† of reproductive potential meets BOTH of the following (a and b):
  - **a)** A negative serum pregnancy test will be confirmed prior to the start of each mobilization cycle and re-confirmed prior to myeloablative conditioning; AND
  - **b)** Patient will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Lyfgenia; OR
- **ii.** A male† of reproductive potential will use an effective method of contraception from the start of mobilization through at least 6 months after administration of Lyfgenia; AND

M) The medication is prescribed by a hematologist or a stem cell transplant physician; AND

N) Current patient body weight has been obtained within 30 days **[documentation required]**; AND

O) If criteria A through N are met, approve one dose of Lyfgenia by intravenous infusion to provide a one-time (per lifetime) single dose, which contains a minimum of 3 x 10^6 CD34+ cells/kg of body weight **[verification required]**.
Note: A single dose of Lyfgenia is composed of one or more infusion bag(s).

† Refer to the Policy Statement.

Dosing. The recommended dose of Lyfgenia is a one-time (per lifetime) single intravenous infusion of a minimum of 3 x 10^6 CD34+ cells per kg of body weight.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Lyfgenia is not recommended in the following situations:

1. **Prior Hematopoietic Stem Cell Transplantation.**
   Note: The prescribing physician must confirm that the patient has not received a prior hematopoietic stem cell transplantation.

Lyfgenia has not been studied in a patient who has received a prior allogeneic or autologous hematopoietic stem cell transplant.[1] Treatment with Lyfgenia is not recommended.

2. **Prior Receipt of Gene Therapy.** Lyfgenia has not been studied in a patient who has received prior gene therapy such as Casgevy™ (exagamglogene autotemcel intravenous infusion). Treatment with Lyfgenia is not recommended.[1]

3. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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2. Kanter J, Walters MC, Krishnamurti WL, et al. Biologic and clinical efficacy of lentiglobin for sickle cell disease. *N Engl J Med*. 2022;3886:617-628.
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5. Centers for Disease Control and Prevention – Sickle cell disease. Available at: https://www.cdc.gov/sickle-cell/. Accessed on January 29, 2026.
6. Patel ZV, Prajjwal P, Bethineedi LD, et al. New modalities and updates in the management of sickle cell disease: a systematic review. *J Blood Med*. 2024;15:435-447.
7. Vertex: Exagamglogene autotemcel (exa-cel) for the treatment of sickle cell disease in patients 12 years and older with recurrent vaso-occlusive crises. FDA Cellular, Tissue and Gene Therapies Advisory Committee. October 31, 2023.
8. Adakveo® intravenous injection [prescribing information]. East Hanover, NJ: Novartis; June 2024.
9. Endari™ oral powder [prescribing information]. Torrance, CA: Emmaus Medical; June 2025.
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11. Siklos® tablets [prescribing information]. Bryn Mawr, PA: Medunik; November 2023.
12. Oxbryta® tablets and tablets for oral suspension [prescribing information]. San Francisco, CA: Global Blood Therapeutics; August 2023.
13. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv*. 2021;5:3668-3689.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	01/31/2024
Selected Revision	**Policy Statement:** The statement regarding verification in claims history for certain criteria was revised to add the qualifier "if claims history is available". The revised statement reads: If claims history is available, verification is required for certain criteria as noted by **[verification in claims history required]**. **Sickle Cell Disease:** **1.** The Note regarding the requirement for no previous gene therapy for sickle cell disease was revised to add the qualifier "(or if claims history is not available)" and to remove "Verify through claims history that the patient has not previously received Lyfgenia or Casgevy (exagamglogene autotemcel intravenous infusion)". The revised Note reads: If no claim for Lyfgenia or Casgevy (exagamglogene autotemcel intravenous infusion) is present (or if claims history is not available), the prescribing physician confirms that the patient has not previously received Lyfgenia or Casgevy. **2.** The criterion regarding cellular screening was revised such that cellular screening is negative for human immunodeficiency virus (HIV)-1 and -2 and negative for Human T-lymphotrophic virus-1 and -2; previously, it was HIV-1 or -2 and human T-lymphotrophic virus-1 or -2. **3.** In the criterion regarding a male* of reproductive potential, the additional phrase in parenthesis, "(i.e., capable of fathering a child)" was removed (not needed). **4.** The criterion regarding current patient weight was revised to remove the qualifier "before intended receipt of Lyfgenia". The revised criterion reads: Current patient body weight has been obtained within 30 days **[documentation required]**.	03/20/2024
Annual Revision	**Sickle Cell Disease:** **1.** The word "cellular" was removed from the criterion regarding screening for certain viruses prior to collection of cells for manufacturing; the new criterion reads: Prior to collection of cells for manufacturing, screening is negative for ALL of the following. **2.** The criterion regarding females/males of reproductive potential was clarified that the criterion pertains to patients of reproductive potential. Previously, the criterion read: "According to the prescribing physician, patient meets ONE of the following"; revised criterion reads: "According to the prescribing physician, a patient of reproductive potential meets ONE of the following".	02/05/2025
Selected Revision	**Sickle Cell Disease:** The requirement that the patient had at least four severe vaso-occlusive crises or events in the previous 2 years was revised such that the definitions of severe vaso-occlusive crises or events are now listed as examples (as a Note) rather than as a specific list as previously in the criteria. The qualifier "Prior to collection of cells for manufacturing" was removed from the requirement regarding screening for certain viruses and the word "Patient" was added. The new criterion now reads: "Patient screening is negative for ALL of the following…".	04/23/2025
Annual Revision	**Sickle Cell Disease:** The dosing was clarified that the recommended dose is a minimum of 3 x 10^6 CD34+ cells per kg. Also, the qualifier regarding body weight "within the past 30 days" was removed. Previously, the dosing was: The recommended dose of Lyfgenia is a one-time (per lifetime) single intravenous infusion of 3 x 10^6 CD34+ cells per kg based on current body weight in kg (within the past 30 days). The new dosing reads: The recommended dose of Lyfgenia is a one-time (per lifetime) single intravenous infusion of a minimum of 3 x 10^6 CD34+ cells per kg of body weight.	02/11/2026